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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,669	01/25/2002	Diane E. Goade	MC-158.USA	9994

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EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,669	GOADE ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *2,3,14,16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, and 4-13, and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I in the paper filed on December 22, 2003 is acknowledged. As noted by the Applicant, the Examiner mistakenly included claims 12 and 13 in the claim listing for this group. The Examiner agrees with the Applicant that the claims that fall correctly within this group are claims 1 and 6-11. Further, the Examiner agrees with the traversal to the extent of the rejoinder of Groups I, III, and IV. Thus, claims 1, and 4-13, and 15 are under examination to the extent that they read on the inventions of claims 1, 4, and 5. Claims 2, 3, 14, 16, and 17 are withdrawn from consideration as drawn to non-elected inventions.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

2. The information disclosure statement filed on March 12, 2002 fails, in part, to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. In the present case, no copies of the Kriesel or the Stanberry Abstracts listed on sheet 3 of the IDS were found with the IDS submissions. These references have therefore not been considered.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 4-13, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. These claims read on methods of determining the effectiveness of a composition either to inhibit Herpes Simplex Virus (HSV) reactivation or as a UV protectant. The methods comprise the making of an animal model of HSV infection by introducing the virus to a surface abrasion, wherein the animal has not been exposed to localized radiation prior to inoculation, allowing the abrasion to heal, administering the composition, exposing the animal to radiation, and determining if the infection is reactivated. The omitted step is the step of correlating the reactivation with the effectiveness of the tested composition for the indicated function (i.e., inhibition of reactivation or protection from UV). The claims indicate that the method is intended to determine the effectiveness of a composition to inhibit reactivation. However, while the claims include a step of determining if the HSV infection is reactivated, they do not identify the relationship between such reactivation and the composition's ability to inhibit the reactivation or protect against UV. Because the claims lack a step of correlation between the reactivation and the compositions functional activity, the claims are rejected as lacking an essential step of the claimed methods.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 4, and 6-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to determine if a composition is effective to prevent HSV reactivation, does not reasonably provide enablement for a method to determine the ability of a composition to inhibit such reactivation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The claims have been described above. For the purposes of this rejection, it is assumed that the claimed method includes a step wherein, if reactivation is detected in step g), then the composition is determined not to inhibit reactivation.

The claims are rejected because the method as claimed, while effective to determine that a composition is not effective in preventing HSV infection reactivation would not be effective to determine if the composition can inhibit reactivation. The term inhibit does not require that the composition completely prevent reactivation. Thus, even if reactivation of the infection is detected in step g), this would not indicate that the composition was ineffective at inhibiting the reactivation, but only that it did not prevent such reactivation. It is suggested that the applicant draft the claims such that the results of step g) are compared to a control, and from a comparison of the results in the test model and the control model determine if the compositions was effective. I.e., the ability of the composition to inhibit reactivation is evidenced where reactivation takes longer or is less severe in the test model than in the control.

7. Claims 1, 4, 6, and 8-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to determine if a composition is effective to

prevent HSV reactivation wherein the radiation used to induce HSV reactivation is ultraviolet radiation, does not reasonably provide enablement for methods where other forms of radiation are used. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These claims, described in part above, indicate that any radiation may be used to reactivate the HSV infections. Cf., claims 1 and 4(referring to exposure of the animals to radiation generally), and claim 7 (limiting the methods to those wherein the radiation is ultraviolet radiation). The indicated claims are rejected because the Applicant has not enabled those in the art to practice the claimed invention using any form of radiation.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The claims and their scope have been described above. The examples provided in specification of this application teach that UV radiation may be used to induce reactivation of HSV infections. See, Example 9. However, the Applicant has not provided any further examples

or guidance as to what other forms of radiation may be used to induce HSV infection reactivation. Further, while the art also indicates that UV radiation induces HSV infection reactivation (see e.g., Norval et al., J Gen Virol 68:2693-98- of record in the March 2002 IDS), it does not indicate that any form of radiation would induce such a reaction. Thus, the claims read on a broad scope of inventions, only a single embodiment of which is supported by the teachings of the art and application. Because the Applicant has not provided any guidance as to what other forms of radiation may be used to induce HSV reactivation, and because those in the art would not be able to practice the full scope of the claimed invention without having to discover for themselves what other forms of radiation would achieve the desired effect, the Applicant is not enabled for the full scope of the claimed invention.

8. Claims 1, and 4-13, and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods wherein a statistically significant number of animals are infected and used, does not reasonably provide enablement for methods involving the use of a statistically insignificant number of animals (e.g. 1, or "two or more"). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The claims have been described above. It is noted that claim 4 refers to the use of two or more, and claim 5 to the determination of a test composition's UV protective effects rather than the anti-HSV reactivation effects. It is further noted that in each example in the specification (see e.g., examples 10, 11, and 15), and in the experiments described in the Norval (supra, at pages 2695-

96), only a portion of the mice exposed to radiation after the resolution of the primary HSV infection suffered from a reactivation of the infection.

From these teachings, it is apparent that a single animal does not provide a sufficient basis either for a HSV reactivation model generally, or to support a conclusion as to the operability of a composition to inhibit HSV reactivation. This is because in any given instance, it is not clear that exposure of a particular animal to UV radiation will induce infection reactivation. In order for the indicated method to be effective, a statistically significant number of animals must be used such that those practicing the invention can be assured that at least a portion of the animals would, if not for the presence of the composition, undergo such reactivation upon exposure to the UV radiation. Therefore, because the teachings of both the application and the art indicate both that multiple animals are required to ensure that a latent infection in at least one will be reactivated, and because those in the art would not be able to determine the efficacy of a particular composition without using multiple animals, the Applicant is not enabled for the scope of the presently claimed inventions.

9. Claims 1, and 4-13, and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods wherein the animal is either a SKH-1 or B6129 mice, does not reasonably provide enablement for methods wherein any animal is used. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The claims read on methods of testing the ability of compositions to perform certain functions based on their ability to inhibit the reactivation of HSV infections by exposure to UV radiation in an

animal model. The Applicant has provided examples of three types of mice, and has shown that two of these models are prone to the required reactivation upon UV exposure after a primary infection has resolved (and not previously exposed to UV radiation). See, application, examples 9 and 15. The Applicant has not, however, provided examples of other animals that may be useful in the claimed inventions.

While the Applicant has indicated that other animals may be used as HSV reactivation models, the application provides no examples of such other animals, or indicated what animals may be useful in the claimed invention. The art however, indicates both the there is variation in the ability of animals to act as models of HSV reactivation. For example, Laycock et al. (Invest Opth & Vis Sci 32: 2741-46- of record in the March 2002 IDS) teaches that mice are better models of HSV latency than rabbits because, whereas rabbits infected with the virus tend to have spontaneous reactivation, mice have low reactivation rates. Page 2741. Thus, this reference shows that the reactivatability of the virus varies among animals, indicating that not every animal would be an effective model in the claimed invention.

This uncertainty in the ability of a particular animal to act as an appropriate model for use in the claimed methods is further illustrated by the teachings of Norval (supra). The teachings of Norval relate the effects of UV radiation of mice infected with HSV through skin abrasions. Page 2695-96. In particular, the reference noted that, in one experiment "recrudescence was also induced in four of 20 pre-irradiated mice and non of 12 non-irradiated mice." The reference therefore indicates that, in the model used in this reference, infection of the mice in the absence of pre-irradiation would not lead to a mouse model that would be effective in the claimed invention. Because the mice used in this reference, which were given the primary infection

through means falling within the scope of the present claims, did not undergo infection reactivation after exposure to UV radiation, they would not be effective models in the claimed methods for determination of HSV reactivation after such UV exposure. It is also noted that Norval states that the variety of mouse used "was found to be critical to the success of inducing recurrence and recrudescence" of HSV infections. Page 2693. The reference cites Harbour et al., (J Gen Virol 55:31-40) in support. Harbour describes experiments which demonstrate that certain mouse varieties are more suitable HSV reactivation models than others, and that reactivation was achieved with all animals. See e.g., Harbour, page 33 Table 2. The art therefore indicates that not every animal, nor every mouse, would make an effective model for the practice of the claimed invention.

While the Applicant has provided two examples of mice in which reactivation according to the claimed method was achieved, the Applicant has not provided any means by which those in the art could distinguish between the animals that would be so useful, and those that would not without having to test each potential model. The Applicant has provided three examples of mice, and shown that UV radiation was effective in reactivating infection in two of these. However, there is not identification of the characteristics of these mice that made them susceptible to such reactivation, nor provision for any other guidance that would lead those in the art to other animals that would be so susceptible. In view of the uncertainty raised by the teachings of the art, and the limited examples and guidance provided by the application, the Applicant has not enabled those in the art to practice the claimed invention using any animal model for HSV reactivation.

10. Claims 5, 6, 8, 10, 11, and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These claims are rejected because the claims do not allow one of ordinary skill in the art to determine whether the composition has UV protection activity or an anti-viral activity. The claims have been described above. They involve the measurement of HSV reactivation after exposure to UV radiation in the presence of the test composition. While the Applicant has indicated that reactivation is indicative of the compositions ability to protect against UV radiation, it is not clear that the ability to inhibit viral reactivation would necessarily indicate that the composition has UV protective capability. For example, Rooney et al. (J Infect Dis 166: 500-506- of record in the March 2002 IDS) teaches that the drug acyclovir was effective in inhibiting the recurrence of HSV infection after exposure to UV radiation. Abstract. See also, Piret et al., Antimicrob Agents Chemother 44(1): 30-38 (teachings that topical administration of the drug was also effective in reducing the severity of HSV reactivation after UV exposure). However, while the art demonstrates that this drug is an effective antiviral agent, and that it would be capable of inhibiting reactivation if tested in the claimed method, there is no evidence that this compound has UV protective activities. Thus, the Applicant has not demonstrated that the ability of a composition to inhibit HSV reactivation in the claimed method is sufficient to determine the effectiveness of that composition as a UV protectant.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1, 4, and 6-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Norval (supra) in view of Wright (U.S. Patent 5,646,155), and further in view of Spruance et al. (Am J Med 85 (Supp 2A): 43-45- of record in the March 2002 IDS) and Rooney et al. (supra). The claims have been described above.

Norval provides teachings regarding murine models of HSV reactivation by UV radiation. Abstract. The reference teaches that the method of administration, in particular the prior exposure of the mouse to UV radiation, affects the rate of reactivation upon later exposure to such radiation. In particular, the reference teaches that reactivation upon exposure to UV radiation was demonstrated in mice exposed to such radiation prior to, and 60 days after the initial exposure to the virus, but that no such reactivation was found in mice not so exposed to UV radiation. See, pages 2694-96. The reference teaches that "the greatest incidence of recrudescence was found in [mice] irradiated with u.v. before infection," but also demonstrates that reactivation was induced in mice that were not so irradiated, so long as irradiation was performed after the primary infection. Thus, while the reference indicates that the method involving UV exposure prior to primary infection may be more effective, the reference nonetheless also renders obvious the use of the model where UV exposure occurs after the infection

Wright teaches the use of a murine HSV-1 reactivation to determine the effect on test compositions on the reactivation of HSV-1 infection. Column 8, lines 36-47. Wright teaches that the infection is reactivated using cellophane tape, and does not specifically teach or suggest the use of UV radiation. Id. However, in describing the method. Wright indicates that compositions "present before and/or during the reactivation stimulus may decrease the degree or erythemia or delay its onset," thereby suggesting that other types of reactivation stimulus may be applied. Further, each of Spruance and Rooney teach that UV radiation can also induce HSV reactivation, and suggest the use of models involving UV radiation induced reactivation for the study of efficacy of antiviral agents. Abstracts. As both taping and UV radiation were known reactivation stimulants (Spruance, page 43), and in view of the suggestion in both Rooney and Spruance that UV reactivation models may be used to study the efficacy of antiviral agents, it would have been obvious to those in the art to substitute one form of reactivation stimulus for the other in the method of Wright.

Because Norval indicates that not every mouse infected and irradiated as described would necessarily suffer recrudescence, it would have been obvious to those in the art to use multiple mice for each test. Because the art indicates that the viral reactivation is the measure of the compositions efficacy, it would have been obvious to those in the art to measure the duration and severity of the reactivated infection as indicators of the anti-reactivation activity of the composition.

13. Claims 5 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Norval, Wright, Rooney, and Spruance as applied above, and further in view of the

teachings of Rooney et al. (Rooney II, Lancet 338: 1419-22- of record in the March 2002 IDS). A claim 5 is treated as representative of the rejected claims. This claim read on a method of determining the efficacy of a composition as a UV protectant wherein the method is identical to those of claims 1 and 4 above. In this claim, the reactivation of the infection is measured to determine the efficacy of the composition as a UV blocker rather than as an antiviral agent. The teachings of the references other than Rooney II have been described above. The references teach methods for the determination of the efficacy of antiviral agents by measuring HSV recrudescence in the animal models, but do not suggest the use of the methods to determine the compositions efficacy as a UV protectant.

Rooney II restates the teachings of the other references that UV is a potent inducer of HSV reactivation. The reference also suggests that a sunscreen may be effective in preventing UV induced recurrent HSV infections. Abstract. Further, the reference teaches that the application of a sunscreen was so effective. Page 1420. Thus, the reference teaches that the application of an effective sunscreen (a UV protectant) is effective at preventing HSV recrudescence. When read in view of the references above, it would have been obvious to those in the art that viral reactivation may be used as a measure either of a compositions efficacy as an antiviral agent, or as an effective sunscreen. Thus, the claimed methods are obvious over the teachings of the indicated combination of references.

Conclusion

14. No claims are allowed.

15. The following prior art reference is made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

Norval et al., Photochem and Photobiol 64(2): 242-45. This reference is redundant to the Norval reference above in that it restates the teachings where 80% of mice that were UV irradiated prior to primary infection later developed recrudescence of the infection after exposure to UV radiation, as opposed to only 20% in mice not irradiated prior to primary infection.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

3/22/04

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